

REMARKS

Claims 1, 2, 4, 7-10 and 16-29 are pending in the present application. Support for the amendments *supra* can be found throughout the specification and claims as filed, for example:

- Non-radiolabeled binding reagent: Patients were immunized with non-radiolabeled antibodies. *See* the Examples.
- Antigens: *See*, lines 9-12 of page 17; lines 3-6 of page 18. The specification at line 6 of page 18 and lines 24-27 of page 19 incorporate by reference U.S. Patent No. 5,075,218 (Jette et al.) and U.S. Patent No. 4,471,057 (Koprowski). Jette et al. disclose a variety of tumor-associated antigens, for example, at lines 20-47 and 37-49 of column 5 and at lines 65-69 of column 16. Koprowski discloses carcinoembryonic antigen (CEA) as a tumor-associated antigen.
- Cancers: *See*, lines 3-6 of page 18. The specification at line 6 of page 18 and lines 24-27 of page 19 incorporate by reference U.S. Patent No. 5,075,218 (Jette et al.) and U.S. Patent No. 4,471,057 (Koprowski). Jette et al. disclose a variety of cancers in Table 1, for example. Koprowski discloses colorectal cancer.
- Routes of administration: *See*, lines 15-29 of page 20.
- Adjuvants/Excipients/Carriers: *See*, lines 1-14 of page 20.
- Antibodies (including fragments): *See*, lines 22-30 of page 18 continuing to lines 1-18 of page 19; and lines 24-27 of page 19.
- Dosage: *See*, pages 22-23 and Example 11.

Applicants assert that no new matter has been added by amendment.

Issues raised in the Office Action will be addressed in the order they were raised by the Examiner.

Priority

1. The Examiner stated at page 2 of the Office Action that the specification of the present application must be updated to indicate the priority claim. Applicants have amended the specification herein to contain a specific reference to applications to which priority is claimed under 35 U.S.C. § 120, including the relationship of the non-provisional applications and the current status of the non-provisional applications as required by 37 C.F.R. § 1.78.

Applicants respectfully bring the Examiner's attention to the transmittal (Exhibit 1) filed with the present application; Box 18 shows that the present application is a continuation of parent application 08/913,290. The Official Filing Receipt, submitted herewith as Exhibit 2, also shows Applicants priority claim to parent application 08/913,290 and PCT application PCT/IB96/00461, filed May 15, 1996. The USPTO has acknowledged that Applicant made the priority claim within the required time period. Thus, Applicants submit that no petition or fee is due. Applicants have amended the specification to contain a specific reference to the priority applications.

Oath/Declaration

2. Applicants herewith submit a new Declaration (in three counterparts) in compliance with 37 C.F.R. 1.67(a) identifying this application by application number and filing date.

35 U.S.C. § 112, second paragraph

3. Claims 1-12 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

- A. The Examiner states at pages 3-4 of the Office Action that "It is unclear if the binding agent must bind to the multi-epitopic reagent while in the serum, or if the binding reagent can bind to the multi-epitopic agent while on the surface of a cell." The claims have been amended to recite administering an antibody that specifically binds to the circulating tumor-associated antigen. Applicants submit that the claims, as amended, are even more definite.
- B. The Examiner states at page 4 of the Office Action that "Claim 1 lacks an active step linking the elicitation of the host immune response to the second epitope with the treatment of cancer as stated in the method objective."

Claim 1 has been amended to recite that an immune response is generated against a second epitope on a circulating tumor-associated antigen produced by cancer cells and elicitation of an immune response against cancer cells producing the antigen. Applicants assert that there is a clear active step linking the method steps and the preamble, which has been amended to recite a method of inhibiting growth of cancer cells.

- C. The Examiner states at page 4 of the Office Action that “Claim 10 lacks an active step linking the elicitation of the immune response against the second epitope of the tumor associated antigen with eliciting a therapeutic immune response as stated in the method objective.” Claim 10 has been amended to recite that a therapeutic immune response is elicited against a second epitope on the tumor-associated antigen, obviating the rejection.
- D. The Examiner states at page 4 of the Office Action that “Claim 12 lacks an active step linking the elicitation of the host immune response with the re-confirming of the antigen as stated in the method objective.” Applicants have cancelled claim 12.

The claims, as amended, even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. § 112, first paragraph, written description

- 4. Claims 1 and 3-12 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner states at page 4 of the Office Action that “The claims are ... reliant upon a genus of binding agents which are not limited in structure, and encompass cells, non-antibody proteins, and non-protein synthetic and natural molecules.”

Applicants respectfully traverse. The specification at lines 22-30 of page 18 and lines 1-17 of page 19 describe a multitude of “binding agents” including, for example, antibodies, antigen-binding fragments, and tumor-binding peptides. Nonetheless, to expedite allowance, Applicants have amended the claims to recite binding agents that are antibodies (including

fragments) (see, e.g., specification at lines 22-30 of page 18 and lines 1-18 of page 19).

Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. § 112, first paragraph, enablement

5. Claim 12 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Applicants have cancelled claim 12, obviating the rejection.

Cited Art

6. The present application has an effective priority date of **May 15, 1996**. The Examiner has cited two (2) references which were published *after* the effective priority date of the instant application, and thus, are not valid as prior art.

- Lanzavecchia (Current Opinion in Immunology, **June 1996**, 8: 348-354). The article by Lanzavecchia was published one (1) month after the priority date of the instant application.
- Madiyalakan et al. (Hybridoma, **1997**, 16: 41-45). The article by Madiyalakan et al. was published one (1) year after the priority date of the instant application.

35 U.S.C. § 102(b)

7. Claims 1-3, 6, 8, 10, and 11 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wagner et al. as evidenced by Lanzavecchia and Simitsek et al. and Jacobs et al.

Claims 3, 6, and 11 have been cancelled, thereby obviating the rejection with respect to these claims.

Applicants have addressed the failure of the Lanzavecchia reference to qualify as cited art for the present application. Accordingly, Applicants further submit that the claims are not anticipated by Wagner et al. as evidenced by Simitsek et al. and Jacobs et al.

The Examiner states that Wagner et al. disclose at pages 86-87, “We do not assume that the infused radiolabeled antibody fragments, having a total amount of radioactivity of

less than 3 mCi could be responsible for the therapeutic effects, since the given dose was at least 40 times lower than that which is normally applied for targeted radiotherapy.” The Examiner also states that Wagner et al. “disclose that the induction of the anti-idiotypic network was responsible for the observed therapeutic effects (abstract).”

Applicants respectfully traverse. While the assumption was made that the radioactivity was not responsible for the therapeutic effects of Wagner et al., no experimental evidence was provided to support this. Moreover, Wagner teaches at the first full paragraph of page 87 that the anti-idiotypic network (i.e., induced Ab3 antibodies) modulate the immune system. However, the Ab3 described in the abstract of Wagner et al. is immunoreactive with the original epitope, not to a second epitope. Finally, Wagner et al. disclose at page 87 that the “anti-idiotypic antibodies can present the critical epitope in a different way and so modulate the immune system of the patient.” In the present claims, binding of the administered antibody (i.e., an Ab1) to the antigen causes an immune response against a second epitope on the antigen, not the Ab2 or Ab3. Furthermore, in the present claims, it is administration of the Ab1 that causes the recognition by the immune system of a previously unrecognizable epitope of the antigen, not the Ab2 as taught by Wagner et al. Applicants submit that the claims of the present invention are novel and non-obvious over the teachings of Wagner et al.

The Examiner uses Lanzavecchia to show an allegedly inherent feature of the radiolabeled antibody fragment as generating a second epitope on the antigen. As stated above, Lanzavecchia was published *after* the effective priority date of the present application and, thus, is not available as art.

The Examiner uses the Simitsek et al. reference to allege that processing of T-cell determinants can be modulated by the presence of a bound antibody.

Applicants respectfully traverse. Simitsek et al. disclose the use of an anti-tetanus antibody immunoreactive with a non-self protein, i.e., tetanus toxin, to induce T cell responses to a second epitope. *See* right column of page 1957. At no point do Simitsek et al. teach or suggest that the antibody in the absence of the antigen would have a therapeutic effect.

Nor do Simitsek et al. teach or suggest the generation of multi-epitopic responses to self proteins wherein tolerance must be broken to induce an effective host immune response.

Simitsek et al. disclose a method to enhance an ongoing immune response to a foreign antigen. Foreign proteins such as those used in the Simitsek et al. publication are readily recognized by the host's immune system and therefore, host tolerance to a self-antigen is not broken.

Simitsek et al. demonstrate activation/proliferation of existing T and B cell clones *in vitro*, but do not teach that the bound antibody/non-self antigen conjugates induce a host immune response *in vivo*. Therefore it can be concluded that the experiments do not show an induction of a therapeutic immune response. Thus, Applicants assert that the Simitsek et al. publication is not enabled for the scope of the claims as currently amended as it does not teach or suggest that an antibody against a self (i.e., tumor-associated) antigen would be therapeutic in the treatment of cancer.

Moreover, Applicants assert that the Examiner cannot use Simitsek in the present rejection as it is not an obviousness rejection. "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

Applicants submit that the rejection is not an obviousness rejection and the teachings of the references cannot be modified or combined. Simitsek teaches a completely different antibody and a completely different antigen. What may or may not be taught by Simitsek does not make up the deficiencies of Wagner et al. At no point do Wagner et al teach or suggest that administration of an Ab1 that specifically binds to a first epitope can generate an a therapeutic immune response to a second epitope. Moreover, just because Simitsek et al. may teach generation of a second epitope *in vitro* does not necessarily mean that the anti-tetanus antibody/antigen complex is capable of generating a therapeutic humoral and/or cellular immune response to said second epitope. Applicants assert that the teachings of a reference cannot be modified in any way to serve as an evidentiary reference in a § 102 anticipatory rejection.

In view of the deficiencies of Wagner et al. as a 102(b) reference, Applicants assert that any evidence which may or may not be provided by Jacobs and Simitsek et al. as to the

inherency of the teachings of Wagner is irrelevant. The instant claims are novel over the prior art for the reasons stated herein, and Applicants respectfully request reconsideration and withdrawal of the rejection.

8. Claims 1-3 and 6-11 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Baum et al. as evidenced by Madiyalakan et al. and Jacobs et al.

Claims 3, 6 and 11 have been cancelled, thereby obviating the rejection with respect to these claims.

The Examiner states at page 11 of the Office Action that “Baum et al. disclose a method for treating ovarian cancer comprising the administration of mAb B43.13 (page 1122, first column, under the heading ‘Monoclonal Antibodies’).”

Applicants respectfully traverse. The section entitled “Monoclonal Antibodies” at the left column of page 1122 actually states that “studies were performed using 1 mg **Indium-111-labeled** F(ab’)2 fragment OC-125 Since 1989, we have primarily used 2 mg **technetium-99m-labeled** intact anti-CA-125 MoAb B43.13.” [Emphasis added] The antibody and OC-125 fragment described by Baum et al. are administered to patients in a radiolabeled form. The claims currently recite administration of a *non-radiolabeled* antibody (i.e., antibody or antigen binding fragment). At no point do Baum et al. teach or suggest using a non-radiolabeled binding agent.

The Examiner states that Madiyalakan is used as an evidentiary reference to show that the monoclonal antibody B43.13 is capable of inducing a CA125 humoral and cellular immune response.

Applicants note that Madiyalakan et al. only describe administration of radiolabeled B43.13 (*See* lines 6-11 of the Introduction). At no point do Madiyalakan et al. teach or suggest that *non-radiolabeled* antibodies would be capable of inducing a therapeutic host immune response. Moreover, in view of the deficiencies of Baum et al. as a 102(b) reference, Applicants assert that any evidence which may or may not be provided by Jacobs and Madiyalakan et al. as to the inherency of the teachings of Baum is irrelevant. The instant

claims are novel over the prior art for the reasons stated herein, and Applicants respectfully request reconsideration and withdrawal of the rejection

35 U.S.C. § 103(a)

9. Claims 1-11 and 16 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chang et al. (EP 153,871) in view of Simitsek et al. and the abstract of Golumbek et al. and Jacobs et al.

Claims 3, 5-6 and 11 have been cancelled, thereby obviating the rejection with respect to these claims.

Chang et al. teach a method of enhancing an immune response *in vivo* to an antigen comprising administering a *complex* of a foreign (i.e., non-self) antigen and an antibody. The claims as currently amended recite administration of an antibody immunoreactive with a tumor-associated (i.e., self) antigen. At no point do Chang et al. teach or suggest an antibody immunoreactive with a self antigen that does not elicit an immune response until tolerance is broken, a method of treating cancer or inducing a therapeutic host immune response by administering antibody.

The Examiner cites the Simitsek et al. reference to allege that processing of T-cell determinants can be modulated by the presence of a bound antibody. Applicants' position regarding Simitsek et al. has been discussed *supra*.

The Examiner uses the Jacobs et al. reference as evidence to show that CA125, CA19.9, and CA15.3 are present on the surface of cancer cells and shed into the blood of cancer patients. Applicants submit that Jacobs et al. fail to teach or suggest that tumor-associated antigens can be multi-epitopic.

The Examiner states at page 13 of the Office Action that the "abstract of Golumbek et al. teach [*sic*] that the goal of immunotherapy is to break tolerance to tumor specific antigens."

Applicants respectfully disagree. Golumbek et al. teach that "approaches have been developed in new animal systems that *modify tumor cells genetically* so that they express new

antigens or secrete certain cytokines. *Engineering tumor cells ... can alter the presentation of tumor antigens.*" [Emphasis added.] At no point do Golumbek et al. teach or suggest administering antibodies or antigen binding fragments thereof immunoreactive with a first epitope on a tumor-associated (i.e., self) antigen, thereby forming an antibody-antigen pair to expose a second epitope on the antigen, wherein an effective immune response is elicited to the second epitope on the antigen.

Applicants assert that the Chang et al. publication does not render the claims obvious as a 103(a) reference, and the deficiencies of Chang et al. cannot be overcome by the teachings of Simitsek et al., Jacobs et al. and Golumbek et al., either alone or in combination. There is no suggestion in Chang et al. to combine the teachings of foreign proteins that are not subject to immune tolerance with Jacobs et al. and Golumbek et al. disclosing and teaching self-antigens. Furthermore, the technologies of enhancing immunity as compared to breaking tolerance to treat cancer are diverse such that it would not motivate one skilled in the art to combine the references. Thus, Applicant asserts that the amended claims are not obvious in view of Simitsek et al. or Golumbek et al., either alone or in combination.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Double Patenting

10. Claims 1-3 and 6-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,241,985.

Applicants' attorneys submit herewith a Terminal Disclaimer on behalf of the Assignee of the instant application over claims 1-14 of U.S. Patent No. 6,241,985 (AREX-P01-005). Applicants respectfully request reconsideration and withdrawal of the rejection.

11. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being patentable over claims 30, 71, 72, 74-76, 85-89, and 91-96 and 98-115 of co-pending Application No. 09/152,698 (AREX-P02-004).

Applicants note that the rejection is provisional, as neither application is in condition for allowance at the present time. Applicants respectfully request that the rejection be held in abeyance until the claims of the instant application or those of co-pending Application No. are in condition for allowance. (MPEP § 804).

12. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being patentable over claims 1-29 of co-pending Application No. 09/994,466 (AREX-P03-002).

Applicants note that the rejection is provisional, as neither application is in condition for allowance at the present time. Applicants respectfully request that the rejection be held in abeyance until the claims of the instant application or those of co-pending Application No. are in condition for allowance. (MPEP § 804).

13. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being patentable over claims 30-38 of co-pending Application No. 09/994,466 (AREX-P03-002) in view of Chang et al. and Simitsek et al. and the abstract of Golumbek et al. and Jacobs et al. and the abstract of Hilken et al.

Applicants note that the rejection is provisional, as neither application is in condition for allowance at the present time. Applicants respectfully request that the rejection be held in abeyance until the claims of the instant application or those of co-pending Application No. are in condition for allowance. (MPEP § 804)

14. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being patentable over claims 119, 120, 125, 129-134, 138-139, 181, 187, 203, 204, 235, 236-239, 242, and 244 of co-pending Application No. 09/376,604 (AREX-P03-004) in view of Jacobs et al.

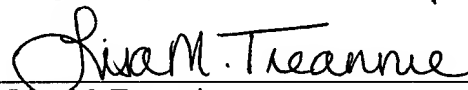
Applicants note that the rejection is provisional, as neither application is in condition for allowance at the present time. Applicants respectfully request that the rejection be held in abeyance until the claims of the instant application or those of co-pending Application No. 09/376,604 are in condition for allowance.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Date: November 15, 2004

Respectfully Submitted,

A handwritten signature in cursive script, reading "Lisa M. Treannie", is written over a horizontal line.

Lisa M. Treannie

Reg. No. 41,368

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Docketing Specialist

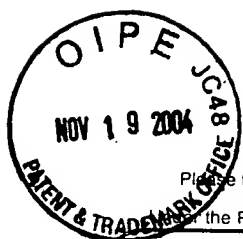
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. 107823-146GON-AREX-P02-005
First Inventor Madiyalakan
Title Method and Composition for Reconforming...
Express Mail Label No. EL538704498US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Applicant claims small entity status.
See 37 CFR 1.27.
3. ☒ Specification [Total Pages 39]
(preferred arrangement set forth below)
 - Descriptive title of the invention
 - Cross Reference to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to sequence listing, a table, or a computer program listing appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
4. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 2]
5. Oath or Declaration [Total Pages 6]
 - a. ☐ Newly executed (original or copy)
 - b. ☒ Copy from a prior application (37 CFR 1.63 (d))
(for continuation/divisional with Box 18 completed)
 - i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s)
named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☐ Application Data Sheet. See 37 CFR 1.76

7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix)
8. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
 - a. ☐ Computer Readable Form (CRF)
 - b. Specification Sequence Listing on:
 - i. ☐ CD-ROM or CD-R (2 copies); or
 - ii. ☐ paper
 - c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement [Power of Attorney]
(when there is an assignee)
11. ☐ English Translation Document (if applicable)
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 [Copies of IDS Citations]
13. ☐ Preliminary Amendment
14. ☐ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
15. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
16. ☐ Request and Certification under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. ☒ Other: Return Postcard

18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP)

of prior application No.: 08 / 913290

Prior application information:

Examiner Ungar

Group Art Unit: 1642

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

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Date Mar 31 2001

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/871,339	05/31/2001	1642	435	187822-146CON	2	15	5

AREX-P02-005

CONFIRMATION NO. 2204

CORRECTED FILING RECEIPT



OC000000007693126

Wayne A Keown
Suite 2900
500 West Cummings Park
Woburn, MA 01801

Date Mailed: 03/21/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

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Antoine A. Noujaim, Edmonton, CANADA;
Richard P. Baum, Hargeshheim, GERMANY;RECEIVED
MAR 27 2002

Domestic Priority data as claimed by applicant

THIS APPLICATION IS A CON OF 08/913,290 03/20/1998 PAT 6,241,885

Foreign Applications

PCT/IB96/00461 05/15/1996

If Required, Foreign Filing License Granted 06/21/2001

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Method and composition for reconfirming multi-epitopic antigens to initiate an immune response

Preliminary Class

**LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15**

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NOT GRANTED

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